REMARKS

I. Status of the Application

Claims 1-8, 10-15 and 37-56 are presently pending in the application. Applicants thank the Examiner for the indication at page 2 of the Office Action that previous rejections of claims (of record) are withdrawn. Claims 1-7, 10, 12-15 and 37-56 stand rejected under 35 U.S.C. § 112, ¶1 as lacking adequate written description. Claims 1-7, 10, 12-15 and 37-56 stand rejected under 35 U.S.C. § 112, ¶1 as lacking enablement. Claims 1-8, 10-15 and 37-56 stand rejected under 35 U.S.C. § 112, ¶2 as being indefinite. Claims 1 and 40 stand rejected under 35 U.S.C. § 102(e) over US 5,472,672 ("Brennan"). Claims 1-8, 10-15, and 37-56 stand rejected under 35 U.S.C. §102(e) over US 5,679,773 ("Holmes"). Claims 1-8, 10-15, and 37-56 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Pat. No. 6,576,425 ("McGall"). Applicants respectfully traverse all rejections in view of the following remarks.

Claims 10 and 50 are currently amended, in part, to correct a recently identified error. Claims 10 and 50 previously indicated that measuring presence of diverse cleaved polymers from the test array was an indicator of the efficiency of the *first* synthesis procedure, and measuring presence of diverse cleaved polymers from the referenced array was an indicator of the efficiency of the *second* synthesis procedure. Claims 10 and 50, as presented above, correctly indicate that the measurement of presence of diverse cleaved polymers from the test array is an indicator of the efficiency of the *second* synthesis procedure, and that that the measurement of presence of diverse cleaved polymers from the reference array is an indicator of the efficiency of the *first* synthesis procedure. Applicants submit that the error was made

unintentionally and in good faith. No new matter is being presented by the foregoing amendment.

II. Claims 1-7, 10, 12-15 and 37-56 Satisfy the Written Description Requirement

Claims 1-7, 10, 12-15 and 37-56 stand rejected under 35 U.S.C. § 112, ¶1 as lacking adequate written description. Applicants respectfully traverse the rejection in view of the amendments and remarks presented here.

A. Applicants were in possession of methods of monitoring polymer array synthesis, including biological polymers at the time of filing.

The Examiner asserts at page 3 of the present Office Action that Applicants were not in possession of polymers other than oligonucleotides and peptides since the specification is said to be directed to peptide (polymers) and nucleotide (polymers) libraries which do not supposedly provide adequate representation of the claimed method of preparing the genus nor representative of a substantial portion of the claimed genus.

In response, Applicants respectfully point out to the Examiner that independent claims 1 and 10 recite by chemical name the building blocks of the claimed biological polymers. Each building block or "mer" is a well-known component of a biological polymer. It is also well known that the "mers" can be chemically connected together to form polymers. Importantly, the array includes biological polymers of diverse sequences, since the purpose of the array is to provide an array of probes that can be used to hybridize to target molecules in, for example, a screening method.

When considered within this context of the claimed invention, the specification need not describe the structural features common to all polymers since they are probes. The specification is consistent with the breadth of the claimed invention. The Examiner's citation to Lilly does not

support a conclusion that the present specification lacks adequate written description for the claimed invention. In Lilly, the claim was to DNA and cDNA and not simply polymers constructed from nucleotides. Accordingly, the Lilly specification needed to provide additional information about the structure, formula, chemical name or physical properties of the DNA or cDNA to demonstrate that the claimed DNA or cDNA would function as DNA or cDNA. In contrast, all Applicants are claiming are biological polymers constructed of well-known building blocks to be used as probes. Applicants respectfully submit that the specification provides ample written description of this aspect of the invention for polymers as well as biological polymers.

For example, Applicants disclose in the beginning of the Summary at page 3, lines 8-10: "the present invention provides methods and compositions to monitor the synthesis and coupling of monomers and polymers to solid substrates, *e.g.* VLSIPS™ arrays." Applicants further disclose shortly thereafter at page 3, line 27 – page 4, line 4:

> The methods are generally suitable to any polymer array, **regardless of the type of polymer.** Thus, the efficiency of synthesis for biological polymers such as proteins, nucleic acids, antigens, and venoms are monitored using the above method. **Non-biological polymers such as carbon chains, vinyls, alcohols, and other polymers are similarly monitored.** The polymer array is typically provided by synthesizing the array on the solid substrate, but the array can also be provided by synthesizing the polymers to be attached to the array in solution, and subsequently attaching the polymers to pre-selected sites in the array. (Emphasis added).

Moreover, Applicants provide a sufficient description of a representative number of species of polymers by actual reduction to practice. Applicants' description of labeling polymers ***for at least 14 pages*** between pages 25 and 39 of the present application is sufficient to convey to skilled artisans that they were in possession of the claimed subject matter at the time of filing. For instance, at page 25, lines 22-27, Applicants state:

> In preferred embodiments, labels of the present invention have the structure A-B, where A is a detectable moiety, and B is a 'linking' or 'bridging' group which comprises one or more functional regions which allow the detectable moiety to be incorporated into a polymer, or attached to one end of the polymer, using chemistry similar to that used to connect monomers into the polymer.

It is more than apparent that the present application evidences Applicants' possession of non-biological polymers at the time of filing.

Further, those of skill in the art certainly would realize that the presently disclosed methods concern not only oligonucleotides and peptides, but also any polymer since oligonucleotides and peptides are just exemplary polymers. The specification provides no reason for those of skill in the art to believe that the synthesis of oligonucleotides and peptides are not comparable to the synthesis of other polymers from a chemical synthesis point of view. The chemistry remains analogous.

III. Claims 1-7, 10, 12-15 and 37-56 Satisfy the Enablement Requirement

Claims 1-7, 10, 12-15 and 37-56 stand rejected under § 112 as not enabling synthesis of spatially defined arrays of diverse polymers. Applicants respectfully traverse this rejection in view of the following discussion.

A. Synthesizing arrays of compounds other than peptides and oligonucleotides would not require undue experimentation.

Applicants established above that the present disclosure adequately demonstrates that Applicants were in possession of the claimed subject matter (synthesizing a preselected array of diverse polymers) at the time of filing. Likewise, through Applicants' teachings and disclosure a person of ordinary skill in the art would understand how to make and use arrays of diverse polymers based on the test set forth in In re Wands. 858 F.2d 731, 737 (Fed. Cir. 1988).

1. **Directi n or Guidance Presented**

First, the Examiner asserts that the specification does not give adequate direction and guidance in the preparation of arrays of diverse polymers since one must be able to control the length of the polymers in the claims to a specified number of monomers. In particular, the Examiner asserts that the chemistry used for the preparation of arrays of (diverse) polymers cannot be done.

In response, Applicants submit that the specification provides guidance in that the polymers added to the array may be previously synthesized polymers, or even commercially available. Applicants also submit that at least the units defined by claims 1 and 10 are readily chemically connected by known synthetic methods to produce polymers.

Second, the Examiner asserts that the specification "has no guidelines for synthesis of spatially defined array of other polymers, since in the synthesis of spatially defined array, protecting and deprotecitng [*sic: deprotecting*] groups are sued [*sic: used*] selectively." Applicants respectfully disagree with this assertion in view of the Applicants' definition of the term "protecting group" at page 16, lines 1-13:

> A "protecting group" as used herein, refers to any of the groups which are designed to block one reactive site in a molecule while a chemical reaction is carried out at another reactive site. More particularly, the protecting groups used herein can be any of those groups described in Green, *et al.*, *Protective Groups In Organic Chemistry*, 2nd Ed., John Wiley & Sons, New York, NY, 1991, which is incorporated herein by reference.

Green *et al.* is a widely accepted treatise for information regarding protecting groups used in organic synthesis – not just for synthesis of biological polymers. In fact, Green admits at page 4: "A review article by Kössell and Seliger discusses protective groups used in oligonucleotide synthesis, including protection of the phosphate group, which is not included in this book, and a series of articles describe various aspects of protective group chemistry." See Tab A. Thus,

Applicants' protecting groups are not limited to protecting groups of biological polymers such as oligonucleotides and peptides.

2. Presence of Working Examples

The Examiner asserts that Applicants have not provided working examples commensurate in scope with the scope of the term "diverse polymers". Applicants note that they need not provide working examples for each and every conceivable polymer that can be made via Applicants' disclosure. Further, as indicated immediately above, a synthetic strategy for the formation of non-biological polymer arrays can employ any of the protecting groups disclosed in Green *et al.*, which are equally applicable to biological polymers and non-biological polymers. In addition, the present disclosure does enable a person of ordinary skill in the art to make arrays of polymers other than peptides and oligonucleotides given the working examples that Applicants *did* provide (see Examples 1-2, pages 41-50).

3. Breadth of Claims

The Examiner states that the breadth of claims encompasses "literally any polymer." However, claims 1 and 10 define biological polymers and recite certain building blocks. As to the term diverse polymer, Applicants disclose at page 15 biological polymers and synthetic polymers suitable for the presently disclosed methods. As mentioned above, Applicants disclose throughout the specification, e.g., in Examples 1-2 at pages 41-50 how the presently disclosed methods can be applied to the presently disclosed polymers. Thus, the specification adequately supports the breadth of the claim terms "biological polymers" and "diverse polymers".

4. State of the Prior Art

The Examiner asserts (without any support) that the state of the prior art is such that methods of preparing polymers limited in the exact number of monomeric units is not widely

practiced except in the nucleotide and peptide areas. Accordingly, one would supposedly have to develop synthetic routes capable of limiting the exact number of monomeric units incorporated into the polymer.

However, the specification teaches those of skill in the art how to make and use arrays of diverse polymers, e.g., at Examples 1-2 at pages 41-50. The Examiner seems to believe that the synthetic route for making an array of diverse polymers necessarily has to be capable of limiting the number of monomeric units incorporated into the polymer, however, none of the claims have this limitation. Regardless, one would presumably be able to control the length of a polymer chain by controlling the amount of monomer present in the reaction. Thus, the state of the art is such that one of ordinary skill would be able to make and use arrays of diverse polymers given the benefit of Applicants' disclosure.

5. Predictability of the Art

While the chemical arts are generally known to be inherently unpredictable, that does not mean that one would not be able to make and use arrays of biological polymers or arrays of diverse polymers. Indeed, it is done everyday in R&D environments. The challenge of determining reaction conditions generic for array synthesis of any type of compound – biological or non-biological – is overcome all the time, as evidenced by many companies producing and selling libraries of biological compounds and non-biological compounds. Thus, the Examiner's assertion regarding the predictability in the art is not compelling.

6. Level of Skill in the Art

It is without a doubt that the level of skill in the pertinent art is high. The Examiner admits this point at page 7 of the Office Action.

Applicants have established through the above analysis with evidence that arrays of polymers other than peptides and oligonucleotides are enabled by Applicants' disclosure. Accordingly, removal of the rejection is requested at this time.

IV. Claims 1-8, 10-15, and 37-56 Are Definite

Claims 1-8, 10-15 and 37-56 stand rejected under 35 U.S.C. § 112, ¶2 for a number of reasons. Applicants traverse each rejection.

First, the Examiner asserts that the term "preselected array" is not clear. Applicants respectfully disagree with the Examiner because the term "preselected array of polymers" is defined at page 15, lines 26-29 as "a spatially defined pattern of polymers on a solid support which is designed before being constructed (i.e., the arrangement of polymers on solid substrate during synthesis is deliberate, and not random)." Certainly, those of skill in the art given the benefit of Applicants' disclosure will readily understand the meaning of the term preselected array.

Second, the Examiner asserts that claims 1 and 40 appear to be incomplete since it is allegedly not clear how the presence of cleaved polymers would indicate the efficiency of the synthesis step. Claims 1 and 40 are complete and do not necessitate the inclusion of an additional step. Claim 1 is as follows:

> 1. (Previously Presented) A method of monitoring polymer array synthesis on a solid substrate comprising:
>
> (i) synthesizing a preselected array of diverse biological polymers connected to cleavable linkers on a solid substrate, whereby the diverse biological polymers occupy different regions of the substrate and are spatially defined on the solid substrate on which the preselected array is synthesized, and wherein the diverse biological polymers comprise nucleotides, nucleosides, phosphoramidites, carbohydrates or natural or synthetic amino acids;

(ii) cleaving diverse biological polymers from the solid substrate by cleaving the cleavable linkers, thereby creating a mixture of diverse unbound biological polymers; and

(iii) measuring presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step.

It is clear that claim 1 would be clear to a person of ordinary skill in the art insofar as step (iii) requires measuring the presence of diverse unbound polymers as an indicator of the synthesizing step. An additional step of measuring a standard is not necessarily required because a person of ordinary skill in the art can interpret such a measurement to determine if synthesis is complete or not. In certain embodiments, the completeness of a reaction can be checked using HPLC, i.e., analyzing the reaction mixture to check for the presence of, for example, starting materials, intermediate materials, desired final products, etc. A person of ordinary skill in the art can interpret the data produced from the HPLC and readily determine if any of the above-referenced materials are present based on the expected reaction products and their respective polarities. For example, in a reverse-phase HPLC, the more polar the compound detected, the shorter the retention time. As such, the additional step allegedly deemed to be required by the Examiner is not necessarily required for claims 1 and 40.

Third, the Examiner asserts at page 8-9 of the present Office Action that "it is not clear how would the method of measuring the cleaved polymers would differ whether the polymers synthesized occupy spatially defined positions on a solid support or they randomly attached to the solid support prior to cleaving and measuring the cleaved polymers. Does applicants mean in the claimed method the spatial position of the polymers is being monitored?"

Applicants interpret the Examiner's assertion to mean that it is not clear whether the claimed method of monitoring polymer synthesis is specific to monitoring predefined arrays or random arrays. Thus, in the context of claim 1, Applicants interpret the Examiner's assertion to

mean that it is not clear whether the step of measuring presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step would differ if one were measuring the presence of polymers cleaved from a preselected array versus a random array.

It is clear that the pending claims pertain to preselected arrays. All pending independent claims (i.e., claims 1, 10, 40, and 50) define in step (i) a preselected array.

The Examiner also asserts that various claims lack antecedent basis. More specifically, the Examiner asserts that the phrase "the labeled unbound polymers" in claims 2-5 have insufficient antecedent basis for this feature in each respective claim or in claim 39. Applicants respectfully indicate that claim 2 does not recite the feature "the labeled unbound polymer." Rather, claim 2 defines "labeled polymers." Thus, the polymers defined by claim 2 are not necessarily characterized as being unbound.

Applicants have amended claim 39 (and similarly amended claim 41) to more clearly define labeled polymers and to provide better antecedent basis for claims 2-5 (and for claims 42-46). As such, Applicants believe this rejection is overcome.

Further, the Examiner asserts at page 9 of the present Office Action that claims 10 and 50 are not clear insofar as the terms "first synthesis protocol" and "second synthesis protocol" are allegedly not clear. Applicants respectfully disagree with this assertion since the definitions of each of these terms are readily determined from their context meaning in the claims. For example, claim 10 is as follows:

> 10. A method for measuring the effect of altering a polymer array synthesis protocol, comprising:
>
> (i) synthesizing a preselected array of diverse biological polymers occupying different regions on a solid support by a first synthesis protocol, wherein the diverse biological polymers are spatially defined on the solid support on which the preselected array is synthesized, **thereby creating a reference array** of biological polymers, wherein the diverse biological polymers

comprise nucleotides, nucleosides, phosphoramidites, carbohydrates or natural or synthetic amino acids;

(ii) synthesizing a preselected array of diverse biological polymers occupying different regions on a solid support synthesized by a second synthesis protocol, wherein the diverse biological polymers are spatially defined on the solid support on which the preselected array is synthesized, and wherein the second synthesis protocol is different than the first synthesis protocol, **thereby creating a test array** of biological polymers;

(iii) cleaving separately the reference array of biological polymers and the test array of biological polymers, thereby creating a mixture of diverse cleaved unbound biological polymers from the reference array and a mixture of diverse cleaved unbound biological polymers from the test array;

(iv) comparing a measurement of presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the second synthesis procedure with a measurement of presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency of the first synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure.

(Emphasis added).

Certainly, those of skill in the art will readily understand that the first synthesis protocol refers to a standard procedure for synthesizing a preselected array (i.e., a reference array), and the second synthesis protocol refers to a test procedure for synthesizing a preselected array (i.e., a test array). Such procedures are disclosed throughout the specification, for example at page 18, lines 11-29. In addition, the synthesis protocols can be performed in a multitude of ways. See, for example, Holmes at column 2, lines 46-64. Not only are there different paradigms for performing solid phase synthesis, but also the protocol within each paradigm can vary. Using standard solid phase synthesis as an example, the protocol can vary, for example, by using one type of resin in a first procedure and another type of resin in a second procedure. Thus, those of skill in the art will readily understand Applicants' use of the terms "first synthesis protocol" and "second synthesis protocol". Accordingly, removal of the present rejection is respectfully requested.

V. Claims 1 and 40 Are Patentable Over Brennan

Claims 1 and 40 stand rejected under § 102(e) over US 5,472,672 ("Brennan"). Applicants respectfully traverse this rejection.

Applicants initially note that cited claims are patentable over Brennan for similar reasons as to why the cited claims are patentable over Lam, which the Examiner indicates at page 2 in the present Office Action as being overcome, because Brennan, like Lam, discloses bead synthesis, which is incapable of serving as a base to support spatially defined diverse polymers.

A. Brennan does not disclose "polymers . . . spatially defined on the solid substrate in which the preselected array is synthesized" because the support Brennan uses for polymer synthesis is not capable of serving as a base to support spatially defined diverse polymers.

First, it is obvious from the disclosure of Brennan at Example 1 (column 15, lines 28-42) that the polymers are not spatially defined on the same substrate used for polymer synthesis:

> 96 well plates were used which have a conical lower section which has been recessed to receive a pressed-fit 0.196 inch filter disk. . . . To each well was added the correct amount of CPG with derivatized first base, either A, T, C, or G.

If the support used for synthesizing the polymers (i.e., the CPG) in Brennan *were* capable of serving as a base to support spatially defined polymers, then the above-cited step of distributing beads of CPG with derivatized first base into the wells of a microtiter plate would not be necessary. Indeed, Brennan places the beads in the microtiter plate to simply contain the solid support used for synthesis (i.e., the CPG beads).

Second, the solid support Brennan uses for polymer synthesis cannot serve as a base to support spatially defined polymers since the support Brennan uses for polymer synthesis, i.e., CPG, cannot support more than one polymer, as discussed immediately below.

Thus, Brennan fails to disclose "polymers . . . spatially defined on the solid substrate in which the preselected array is synthesized."

B. Brennan does not disclose "a preselected array of diverse polymers...on a solid support" because Brennan teaches bead synthesis, which is incapable of forming an array of diverse polymers on a solid support in which the preselected array is synthesized.

Applicants define at page 15, lines 26-29, a preselected array of polymers as ". . . a spatially defined pattern of **polymers** on **a** solid support which is designed before being constructed. . ." (Emphasis added). Thus, a preselected array is characterized by having ***more than one polymer on a single solid support.***

Brennan teaches throughout its disclosure bead synthesis, otherwise known as solid phase synthesis, which is fundamentally different from the array synthesis disclosed by Applicants. One fundamental difference is that bead synthesis is limited to there being only one polymer per solid support (i.e., the bead). Applicants explained the distinction between bead synthesis and array synthesis in the previous Amendment and Response dated 4/16/03, which is incorporated here by reference for all purposes. Nowhere does Brennan disclose more than one distinct polymer species being synthesized on an individual bead. Indeed, it is readily apparent from Example I at column 13, line 47 – column 14, line 5 that Brennan only contemplates synthesizing a single oligonucleotide on a single solid support:

> In general, the basic steps of the synthesis reaction are as follows, with appropriate acetonitrile washing steps:
> a) the first nucleoside, which has been protected at the 5' position, is derivatized to a solid support, usually controlled pore glass (CPG), or is obtained prederivatized;
> b) the sugar group of the first nucleoside is deprotected or detritlyated, using tricholoraceticmethylene chloride acid, which results in a colored product which may be monitored for reaction progress;
> c) the second nucleotide, which has the phosphorus, sugar and base groups protected, is added to the growing chain, usually in the presence of a tetrazole catalyst;
> d) unreacted first nucleoside is capped to avoid perpetuating errors, using acetic anhydride and N-methylimidazole;
> e) the phosphite triester is oxidized to form the more stable phosphate triester, usually using iodine reagents;

f) the process is repeated as needed depending on the desired length of the oligonucleotide; and
g) cleavage from the solid support is done, usually using aqueous ammonia at elevated temperatures over a period of hours.

Clearly, as mentioned above, if the CPG bead were capable of providing spatial addressability, then there would not be a need for Brennan to add the CPG beads to wells in a microtiter plate. It is apparent then that the method of Brennan cannot have more than one polymer on a single solid synthesis support. Even if one were to argue that the solid support disclosed by Brennan does have more than one (albeit the same) polymer on the solid support, there certainly cannot be ***diverse*** polymers on the same single support. This is because of the inherent limitation in bead synthesis described above.

Thus, Brennan does not disclose a preselected array of diverse polymers because the support Brennan uses for bead polymer synthesis cannot support an array of (more than one) diverse polymers. Since Brennan does not disclose a preselected array of diverse polymers, it naturally follows that Brennan also does not disclose or otherwise teach or suggest diverse polymers occupying different regions of the substrate, as defined by Claim 40.

Applicants submit that Claim 40 (the broadest pending independent claim) is patentable over Brennan because Brennan does not disclose or otherwise teach or suggest at least the claim elements discussed immediately above. Claim 40 is reproduced below:

40. (Previously Presented) A method of monitoring polymer array synthesis on a solid substrate comprising:
(i) synthesizing a preselected array of diverse polymers connected to cleavable linkers on a solid substrate, whereby the diverse polymers occupy different regions of the solid substrate and are spatially defined on the solid substrate in which the preselected array is synthesized;
(ii) cleaving diverse polymers from the solid substrate by cleaving the cleavable linkers, thereby creating a mixture of diverse unbound polymers; and

(iii) measuring presence of diverse unbound polymers as an indicator of the efficiency of the synthesizing step.

Thus, removal of the present rejection is respectfully requested at this time.

VI. Claims 1-8, 8-15, and 37-56 Are Patentable over Holmes

Claims 1-8, 10-15, and 37-56 stand rejected under 35 U.S.C. §102(e) over Holmes. Applicants respectfully traverse this rejection in view of the following comments.

At the outset, Applicants note that the Examiner is presently applying Holmes by itself, whereas, in previous Office Actions, the Examiner relied on a combination of Holmes and Lam. In prior responses, Applicants overcame the rejections based on this combination.

Nevertheless, all pending claims are patentable over Holmes at least because **Holmes fails to disclose measuring the presence of diverse unbound polymers as an indicator of the efficiency of the synthesizing step**, as recited in claims 1 and 40. Similarly, Holmes also fails to teach or suggest comparing a measurement of presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the second synthesis procedure with a measurement of presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency of the first synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure, as recited in claims 10 and 50.

Instead, Holmes discloses the confirmation of synthesis fidelity by comparison with known standards. See Column 19, lines 34-55. Holmes provides no guidance as to ***how*** the synthesis fidelity should be determined. At best, Holmes discloses at column 22, lines 16-23 that following synthesis, the labeled species can be subjected to HPLC and the resultant

chromatogram can be compared with a standard. Applicants note, however, that chromatogram obtained by HPLC in Holmes is not being used to indicate the efficiency of the synthesizing step, as defined by all pending claims. Rather, Holmes is using HPLC to confirm the presence of the desired reaction product. This distinction between Holmes and the present application is abundantly clear at Example 7 in Holmes (column 29, line 39 – column 30, line 21) where Holmes indicates that after synthesis, collected filtrates were analyzed by HPLC to detect the presence of thiazolidinone. It important to note that the disclosure of Holmes is limited to using HPLC to determine synthesis fidelity *after* the reaction is complete, whereas, the present methods are advantaged by using HPLC to indicate the efficiency of the synthesizing step *both during and after* the synthesizing step. Thus, all pending claims are patentable over Holmes for at least the foregoing reasons.

Further, Holmes does not suggest or even hint comparing a measurement of presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the second synthesis procedure with a measurement of presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency of the first synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure, as defined by claims 10 and 50. That is, Holmes does not disclose element (iv) of claims 10 and 50. As discussed above, Holmes merely discloses comparing the resultant chromatogram with a chromatogram from a standard that is synthesized by alternative methods. Holmes does not disclose comparing both (1) a measurement of presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the second synthesis procedure with (2) a measurement of presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency

of the first synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure. Nowhere does Holmes disclose that the efficiency of the reference or standard synthesis procedure is measured as an indicator of its efficiency. Thus, in no way does Holmes disclose measuring presence of diverse cleaved polymers *twice* (i.e., of a test array and a reference array). As such, independent claims 10 and 50, and all claims dependent therefrom are patentable over Holmes for this additional, independent reason.

In view of the foregoing remarks, Applicants believe the rejection to be improper and request withdrawal of the present rejection and allowance of all pending claims.

VII. Claims 1-8, 10-15, and 37-56 Are Patentable over McGall

Claims 1-8, 10-15, and 37-56 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 7-45 of McGall. Applicants are submitting herewith a terminal disclaimer, which, as the Examiner indicates at page 12 of the Office Action, can be used to overcome an obviousness-type double patenting rejection. As such, the present rejection is overcome.

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VIII. Conclusion

Applicants have shown that Brennan and/or Holmes neither anticipate nor render the pending claims obvious. Further, Applicants have clearly demonstrated that the specification as filed meets the enablement, written description, and definiteness requirements of § 112. Having addressed all outstanding issues, Applicants respectfully request allowance of the case at this time. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

Dated: December 5, 2003

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PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

Second Edition

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and

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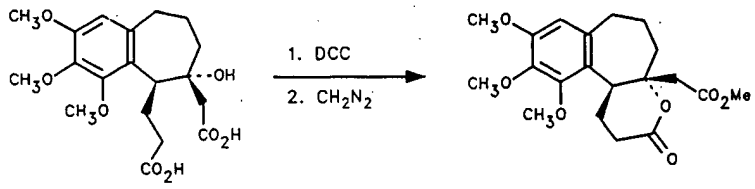
Internal protection, used by van Tamelen in a synthesis of colchicine, may be appropriate:[30]



Selection of a Protective Group from This Book

To select a specific protective group, the chemist must consider in detail all the reactants, reaction conditions, and functionalities involved in the proposed synthetic scheme. First he or she must evaluate all functional groups in the reactant to determine those that will be unstable to the desired reaction conditions and require protection. The chemist should then examine reactivities of possible protective groups, listed in the Reactivity Charts, to determine compatibility of protective group and reaction conditions. The protective groups listed in the Reactivity Charts (see Chapter 8) have been used most widely; consequently, considerable experimental information is available for them. The chemist should consult the complete list of protective groups in the relevant chapter and consider their properties. It will frequently be advisable to examine the use of one protective group for several functional groups (i.e., a 2,2,2-trichloroethyl group to protect a hydroxyl group as an ether, a carboxylic acid as an ester, and an amino group as a carbamate). When several protective groups are to be removed simultaneously, it may be advantageous to use the same protective group to protect different functional groups (e.g., a benzyl group, removed by hydrogenolysis, to protect an alcohol and a carboxylic acid). When selective removal is required, different classes of protection must be used (e.g., a benzyl ether, cleaved by hydrogenolysis but stable to basic hydrolysis, to protect an alcohol, and an alkyl ester cleaved by basic hydrolysis but stable to hydrogenolysis, to protect a carboxylic acid).

If a satisfactory protective group has not been located, the chemist has a number of alternatives: rearrange the order of some of the steps in the synthetic scheme so that a functional group no longer requires protection or a protective group that was reactive in the original scheme is now stable; redesign the synthesis, possibly making use of latent functionality[31] (i.e., a functional group in a precursor form; e.g., anisole as a precursor of cyclohexanone). Or it may be necessary to include the synthesis of a new protective group in the overall plan.

A number of standard synthetic reference books are available.[32,33] A review article by Kössell and Seliger[34] discusses protective groups used in oligonucleotide syntheses, including protection for the phosphate group, which is not included in this book, and a series of articles[35] describe various aspects of protective group chemistry.